Remarks

Claims 1-61 are currently pending in this application. Claims 11, 49, 52, 53, 56, and 59 are amended. Claims 50, 51, and 54 are canceled. Claims 3, 4, 6-9, 12-31, 39, 41, 43, 45, 60, and 61 are withdrawn from consideration as being drawn to non-elected inventions.

1. Correction of Claims

The Action indicated that SEQ ID NO: 75 is recited in claim 46 as human light chain CDR3 and in claim 53 as human heavy chain CDR2, and that SEQ ID NO: 73 is recited in claim 47 as human light chain CDR2 and in claim 54 as human heavy chain CDR3. As pointed out by the Action, SEQ ID NO: 75 and SEQ ID NO: 73 are light chain CDRs. The claims as amended now properly refer to the sequences that are the heavy and light chain CDRs. The specification has also been amended to correct this typographical error.

2. Claim Rejections - 35 USC §112, first paragraph, Enablement

Claims 1, 2, 5, 10, 11, 32-38, 40, 42, 44, 46-54, and 56-59 stand rejected under 35 USC §112, first paragraph as not enabled for an isolated human antibody that specifically binds to interleukin-1 receptor type 1 (IL-1R1) or an immunologically functional fragment thereof, with the heavy chain SEQ ID NO: 16; an isolated human antibody that specifically binds to IL-1R1 or an immunologically functional fragment thereof, with the light chain SEQ ID NO: 18; an isolated human antibody with a human heavy chain CDR3 region SEQ ID NO: 69 and a human light chain CDR3 region SEQ ID NO: 75; an isolated human antibody with a human heavy chain CDR2 region SEQ ID NO: 66 and a human light chain CDR2 region SEQ ID NO: 73; an isolated human antibody with a human heavy chain CDR1 region SEQ ID NO: 63 and a human light chain CDR1 region SEQ ID NO: 71; an isolated human antibody that specifically binds IL-1R1 with a human heavy chain CDR1 region SEQ ID NO: 63; an isolated human antibody that specifically binds IL-1R1 with a human heavy chain CDR2 region SEQ ID NO: 66; an isolated human antibody that specifically binds IL-1R1 with a human heavy chain CDR1 region SEQ ID NO: 69; an isolated human antibody that specifically binds IL-1R1 with a human light chain CDR1 region SEQ ID NO: 71; an isolated human antibody that specifically binds IL-1R1 with a human light chain CDR2 region SEQ ID NO: 73; an isolated human antibody that specifically

binds IL-1R1 with a human light chain CDR3 region SEQ ID NO: 75; an isolated human antibody that specifically binds to IL-1R1 with at least 90% sequence identity to heavy chain SEQ ID NO: 16 and with at least a 90% sequence identity to light chain SEQ ID NO: 18; an antibody that specifically binds Epitope 4 of IL-1R1, an immunologically functional fragment therof, of an IgG2 antibody with the heavy chain SEQ ID NO: 16 and a light chain SEQ ID NO: 18; an immunologically functional fragment thereof, of an antibody that binds specifically to the polypeptide of SEQ ID NO: 76; and an immunologically functional immunoglobulin fragment thereof, of an antibody that binds specifically to Epitope 4 of IL-1R1.

To satisfy the enablement requirement, an applicant must enable one of ordinary skill in the art to make and use the claimed invention. Enablement is decided with a view towards a weighing of the *Wands* factors, including (1) the quantity of experimentation required, (2) the amount of guidance presented, (3) the presence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the skill of those in the art, (7) the predictability of the art, and (8)the breadth of the claims. *In re Wands,* 8 USPQ2d 1400 (Fed. Cir. 1988) However, enablement is not precluded by the necessity of even a considerable amount of experimentation in some cases, particularly if the experimentation is routine in nature, even when the art may be unpredictable. *U.S. v. Telectronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988); *Ex Parte Mark*, 12 USPQ2d 1904(BPAI 1989); *In re Angstadt and Griffin*, 190 USPQ 214 (CCPA 1976). Moreover, some unpredictability of the outcome of experimentation does not make the experimentation undue since an experiment would hardly be done if its outcome was known beforehand. *In re Angstadt and Griffin*, 190 USPQ 214 (CCPA 1976).

The Action asserts that antibody binding and specificity *require* a heavy and light chain, each chain having three CDRs. Consistent with this position, the Action indicated that the specification was enabling for isolated human antibodies that specifically bind IL-1R1 comprising a heavy chain variable region of SEQ ID NO: 16 and a light chain variable region of SEQ ID NO: 18, or an antigen binding fragment thereof, an antibody that has three heavy chain CDRs (SEQ ID NO: 63, SEQ ID NO: 66, and SEQ ID NO: 69) and three light chain CDRs (SEQ ID NO: 71, SEQ ID NO: 73, and SEQ ID NO: 75), and an isolated human antibody that binds to SEQ ID NO: 76. Therefore, Applicants respectfully contend that claims 5 and 10 drawn to antibodies having both the heavy and light chain variable regions (SEQ ID NO: 16 and SEQ ID

NO: 18), amended claim 53 drawn to antibodies having three heavy chain CDRs (SEQ ID NO: 63, SEQ ID NO: 66, and SEQ ID NO: 69) and three light chain CDRs (SEQ ID NO: 71, SEQ ID NO: 73, and SEQ ID NO: 75), and claim 55 drawn to antibodies that bind SEQ ID NO: 76, are all enabled.

Regarding the Action's assertion that antibody binding and specificity *require a heavy and light chain, each chain having three CDRs*, Applicants note that it may be true that both heavy and light chain variable regions are necessary for antigen binding *in some cases*, however, single variable regions capable of antigen binding can be selected. For example, US Patent No. 6,248,516 describes making and testing heavy chain variable regions for binding to an antigen, where the inventors found that some heavy chain variable regions could bind to the antigen, in this case lysozyme, in the absence of a light chain (see US Patent No. 6,248,516 Example 5, col. 24-26, and Example 6, col. 26-27). The 6,248,516 patent also predicts that similar results should be obtainable using light chain variable regions (see US Patent No. 6,248,516, Example 11, col. 32). The patent also describes improving the binding affinity of a heavy chain variable region by mutagenesis of only amino acids within the CDR3 of a heavy chain variable region (see US Patent No. 6,248,516, Example 7, col. 28-30). Further, it is known that some naturally-occurring antibodies contain heavy chains and lack light chains entirely (*See e.g.,* Desmyter et al. (2001), J. Biol. Chem. 276(28): 26285-90). Therefore, it has been demonstrated in the art and those of skill in the art will recognize that heavy chain variable regions can bind to an antigen in the absence of light chains, and similar results have been predicted for light chain variable regions.

Further, it is known that alteration of only a heavy or a light chain CDR3 or both can alter the binding affinity of an antibody (*See e.g.* Schier et al., 1996, J. Mol. Biol. 263: 551-67; Desiderio et al., 2001, J. Mol. Biol. 310: 603-15), and those skilled in the art know that a heavy chain CDR3 can determine the binding specificity of an antibody. For example, human antibodies with binding specificity similar to that of a known murine antibody have been selected using a scheme in which the heavy chain CDR3 was the only sequence required to be retained (Klimka et al., 2000, British J. Cancer 83(2): 252-260). The selection described by Klimka et al. produced antibodies, which had the binding specificity of the murine antibody, with sequences that diverged substantially from the murine heavy and light chain variable regions sequences, except at the heavy chain CDR3. As another example, Ditzel et al. (1996, J. Immunol. 157:739-

49) show that transplantation of only a heavy chain CDR3 from a polyreactive antibody to monospecific antibody transformed the monospecific antibody into a polyspecific antibody (see Ditzel et al., at p.742-45, Fig.3).

Moreover, Beiboer et al. (2000, J. Mol. Biol. 296: 833-49) succeeded in humanizing murine antibodies with a desired binding specificity using a "guided selection" procedure that required that the heavy chain CDR3 be retained and that the binding specificity of the antibody be maintained. Beiboer et al. succeeded in finding an antibody having the original binding specificity, which retained the original heavy chain CDR3, but not the original light chain CDR3. In addition, Barbas et al. (1995, Proc. Natl. Acad. Sci. USA 92: 2529-33) successfully transplanted the heavy chain CDR3 from an antibody that bound to DNA into an unrelated antibody to generate an antibody that binds to DNA with an affinity very similar to that of the original antibody. Finally, Rader et al. (1998, Proc. Natl. Acad. Sci. USA 95: 8910-15) show that a humanization scheme that involves retaining only the heavy and light chain CDR3s rapidly generated antibodies with binding affinity and specificity similar to that of an original murine antibody.

These references indicate that a heavy chain CDR3, alone, can determine the binding specificity and affinity of an antibody of which it is a part. Thus, a claim directed to a heavy and/or a light chain CDR3 or variable region can have sufficient information to specify the portion of an antibody critical for binding. Consequently, in view of the art recognized examples discussed above, claims having limitations directed only to a heavy or light chain variable region or CDR3 are enabled, including claims 1 and 2 drawn to antibodies comprising a particular light or heavy chain; claim 46 drawn to antibodies comprising a particular heavy chain CDR3 and a particular light chain CDR3; claims 47 and 48, and amended claims 49 and 52, which include the particular heavy chain CDR3 and particular light chain CDR3.

The Action also asserts that the term "immunologically functional immunoglobulin fragment" is not enabled because the specification does not provide examples of antibodies that could be used by those of skill in the art to make "immunologically functional immunoglobulin fragment." As pointed out by the Action, Applicants define "immunologically functional immunoglobulin fragment" on page 17 of the specification as "a polypeptide fragment that

contains at least the variable domains of the immunoglobulin heavy and light chains." The Action specifically asserts that one of skill in the art "could not make the claimed 'immunologically functional immunoglobulin fragment' in the absence of the appropriate starting materials." Applicants respectfully contend that the starting materials are the antibodies in the claims, from which the "immunologically functional immunoglobulin fragment" is derived. The term "immunologically functional immunoglobulin fragment" specifically relates to the antibodies of claims 1, 2, 5, and 10. The antibodies of these claims, as discussed above, are enabled. Thus, one of skill in the art would readily recognize the starting materials and could readily make the claimed "immunologically functional immunoglobulin fragments."

The Action also rejects claim 11 as not enabled, because it encompasses an antibody with "at least 90% sequence identity." Specifically, the Action indicates that the claims lack recitation of "a testable function and limitations regarding the sequence length over which the percent identity is required." Claim 11 has been amended to recite "wherein the antibody inhibits binding of either IL-1β or IL-1ra to IL-1R1," thus providing a testable function, which is supported in the specification (*e.g.* Example 3). The length limitation is inherently provided in the claim itself, since the percent identity is to the amino acid sequence as set forth in SEQ ID NO: 16 and SEQ ID NO: 18, both of which have a defined length as shown in the Sequence Listing. Consequently, claim 11 is enabled.

In addition, the Action rejects claims 56 and 59, because the claims encompass antibodies that bind Epitope 4, which contains only three amino acids. The Action specifically asserts that an epitope must have at least six amino acids. Claims 56 and 59 have been amended to recite that the antibody binds "the amino acid sequence YSV of IL-1R1." The specification provides exemplary antibodies that bind IL-1R1 through the sequence YSV (see Examples 5 and 9). Thus, claims 56 and 59 are enabled.

Therefore, in view of the above discussion, Applicants submit that the claims are enabled, and respectfully request that these grounds of rejection be withdrawn.

3. Claim Rejections - 35 USC §112, first paragraph, Written Description

Claims 1, 2, 5, 10, 11, 32-38, 40, 42, 44, 46-54, and 56-59 stand rejected under 35 USC

§112, first paragraph for failing to comply with the written description requirement. The Action asserts that Applicants are not in possession of an isolated human antibody that specifically binds to interleukin-1 receptor type 1 (IL-1R1) or an immunologically functional fragment thereof, with the heavy chain SEQ ID NO: 16; an isolated human antibody that specifically binds to IL-1R1 or an immunologically functional fragment thereof, with the light chain SEQ ID NO: 18; an isolated human antibody with a human heavy chain CDR3 region SEQ ID NO: 69 and a human light chain CDR3 region SEQ ID NO: 75; an isolated human antibody with a human heavy chain CDR2 region SEQ ID NO: 66 and a human light chain CDR2 region SEQ ID NO: 73; an isolated human antibody with a human heavy chain CDR1 region SEQ ID NO: 63 and a human light chain CDR1 region SEQ ID NO: 71; an isolated human antibody that specifically binds IL-1R1 with a human heavy chain CDR1 region SEQ ID NO: 63; an isolated human antibody that specifically binds IL-1R1 with a human heavy chain CDR2 region SEQ ID NO: 66; an isolated human antibody that specifically binds IL-1R1 with a human heavy chain CDR1 region SEQ ID NO: 69; an isolated human antibody that specifically binds IL-1R1 with a human light chain CDR1 region SEQ ID NO: 71; an isolated human antibody that specifically binds IL-1R1 with a human light chain CDR2 region SEQ ID NO: 73; an isolated human antibody that specifically binds IL-1R1 with a human light chain CDR3 region SEQ ID NO: 75; an isolated human antibody that specifically binds to IL-1R1 with at least 90% sequence identity to heavy chain SEQ ID NO: 16 and with at least a 90% sequence identity to light chain SEQ ID NO: 18; an antibody that specifically binds Epitope 4 of IL-1R1, an immunologically functional fragment therof, of an IgG2 antibody with the heavy chain SEQ ID NO: 16 and a light chain SEQ ID NO: 18; an immunologically functional fragment thereof, of an antibody that binds specifically to the polypeptide of SEQ ID NO: 76; and an immunologically functional immunoglobulin fragment thereof, of an antibody that binds specifically to Epitope 4 of IL-1R1.

The Action indicated that Applicants are in possession of an isolated human antibody that specifically binds IL-1R1 comprising a heavy chain variable region of SEQ ID NO: 16 and a light chain variable region of SEQ ID NO: 18, or an antigen binding fragment thereof, an antibody that has three heavy chain CDRs (SEQ ID NO: 63, SEQ ID NO: 66, and SEQ ID NO: 69) and three light chain CDRs (SEQ ID NO: 71, SEQ ID NO: 73, and SEQ ID NO: 75), and an isolated human antibody that binds to SEQ ID NO: 76. Therefore, Applicants respectfully contend that claims 5 and 10 drawn to antibodies having both the heavy and light chain variable

regions (SEQ ID NO: 16 and SEQ ID NO: 18), amended claim 53 drawn to antibodies having three heavy chain CDRs (SEQ ID NO: 63, SEQ ID NO: 66, and SEQ ID NO: 69) and three light chain CDRs (SEQ ID NO: 71, SEQ ID NO: 73, and SEQ ID NO: 75), and claim 55 drawn to antibodies that bind SEQ ID NO: 76, all satisfy the written description requirement.

To satisfy the written description requirement an applicant must "convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention.* The invention is, for purposes of the "written description" inquiry, *whatever is now claimed.*" *Vas Cath v. Mahurkar,* 19 USPQ2d 1111 (Fed. Cir. 1991). Generally, what must be described is a "complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." *Enzo v. Gen-Probe*, 3 USPQ2d 1609 (Fed. Cir. 2002). "It is not correct, however, that all functional descriptions of genetic material fail to meet the written description requirement." *Enzo, supra.* Further, the description of a genus may be adequate when only one species within the genus is disclosed, particularly in predictable arts. *Bilstad v. Wakalopulos,* 386 F.3d 1116, 1124-1126, 72, USPQ2d 1785 (Fed. Cir. 2004). As stated above, the art of making antibodies has been recognized as a mature, and thus relatively predictable, art, *Noelle v. Lederman,* 69 USPQ2d 1508 (Fed. Cir. 2004). In less predictable arts, description of more species within a claimed genus can be necessary to show possession of the genus. *Bilstad,* at 1125.

Regarding the percent identity, Example 14 of the Written Description Guidelines indicates that variants of a protein are adequately described where the specification indicates that the variant has a certain percentage identity to a particular protein sequence, wherein the variant retains the activity of the unchanged protein, and wherein the specification demonstrates the activity of the unchanged protein, thereby providing an assay for identifying the variants with the claimed activity.

Regarding "immunologically functional immunoglobulin fragments," methods for truncating proteins are well known in the art, and the specification provides assays for testing activity of the claimed antibodies and "immunologically functional immunoglobulin fragments." As discussed above, the starting material for the "immunologically functional immunoglobulin

fragments" are the antibodies of the claims. Thus, one of skill in the art would recognize that Applicants were in possession of "immunologically functional immunoglobulin fragments" of the claimed antibodies at the time the application was filed.

The Action specifically asserts that the Applicants have not described the structural characteristics of the antibodies of the claims by "broadly claiming an antibody by only reciting the heavy chain or only the light chain, or only the specific combination of heavy and light chain for the CDR1, 2, or 3 CDR regions, or only one of the 6 specific CDR regions of the heavy or light chain." Also, the Action asserts that there is insufficient written description for an "immunologically functional immunoglobulin fragment thereof," antibodies that have at least a 90% sequence identity to heavy chain SEQ ID NO: 16 and light chain SEQ ID NO: 18; and to antibodies that specifically bind Epitope 4.

The Action asserts that one of skill in the art cannot envision all contemplated antibodies of the instant claims, because the claims recite only a heavy chain variable region, or only a light chain variable region, or only certain CDRs. As discussed above, those of skill in the art recognize that CDR3s alone, heavy chain variable regions alone, and light chain variable regions alone can bind to an epitope and/or can affect binding specificity of an antibody to a particular epitope. Although the Action asserts that antibodies must have a light chain, a heavy chain, and all six CDRs from the light and heavy chains, Applicants have provided evidence that those skilled in the art recognize that this is not always the case.

The instant specification provides evidence of actual possession of plural species of antibodies that bind IL-1R1, including 15C4, 26F5, 27F2, 24E12, and 10H7. Applicants specifically describe the variable regions of these antibodies, the CDRs of these antibodies (see, for example, Figures 10 and 11), describe functional assays demonstrating activity of these antibodies (see, for example, Examples 3 and 4), and describe epitopes for these antibodies (see, for example, Examples 5 and 9). Thus, Applicants have adequately described numerous heavy and light chain variable regions and CDRs that bind to IL-1R1 and that bind to the amino acid sequence YSV. The claims encompass antibodies that comprise these heavy and light chain variable regions, antibodies that comprise CDR3 of both the heavy and light chains, and antibodies that bind the amino acid sequence YSV. All of the claims require that the antibodies

specifically bind to IL-1R1. The Action asserts that one of skill in the art cannot envision all contemplated antibodies of the instant claims, because the claims recite only a heavy chain variable region, or only a light chain variable region, or only certain CDRs. However, one of skill in the art will recognize that the claims are not drawn to antibodies that could also comprise *any* heavy or light chain variable region or *any* CDR, but only to those heavy and light chain variable regions or CDRs that will still allow for binding to IL-1R1. The specification provides assays that will identify these antibodies.

As discussed above, the art of making antibodies is considered to be more mature, *i.e.*, more predictable, than some other areas of biotechnology. Consequently, the disclosure of plural species within the scope of many of the rejected claims, along with the predictable nature of the art, would lead one of skill in the art to conclude that Applicants were in possession of the common attributes of the claimed antibodies. Therefore, Applicants submit that the claims satisfy the written description requirement, and respectfully request that this ground of rejection be withdrawn.

4. Claim Rejections - 35 USC §102

Claims 55 and 56 stand rejected under 35 USC §102(e) as being anticipated by US Patent No. 6, 511, 665 (the '665 patent). The Action asserts that the '665 patent teaches SEQ ID NO: 76. MPEP 2131 points out that "a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. Claim 55 encompass human antibodies that specifically bind to SEQ ID NO: 76. The '665 patent, however, does not explicitly or implicitly teach antibodies that bind to the amino acid sequence of SEQ ID NO: 76. Rather, the '665 patent teaches the amino acid sequence of IL-1 receptor, which comprises SEQ ID NO: 76, and the production of monoclonal antibodies to *the entire coding region* of the human IL-1 receptor. There is no indication that the antibodies bind to the amino acid sequence of SEQ ID NO: 76. Since the '665 patent does not explicitly or implicitly indicate that the amino acid sequence of SEQ ID NO: 76 could, should, or was used to generate antibodies, the '665 patent cannot anticipate the instant claims. Consequently, Applicants respectfully request that this ground of rejection be withdrawn.

CONCLUSION

Applicants respectfully contend that all conditions of patentability are met in the pending claims as amended or as originally presented. Allowance of the claims is thereby respectfully solicited.

The Examiner in charge of this application is invited to contact the undersigned representative as indicated below if it is believed to be helpful.

Respectfully submitted,
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